Towards efficient methods to construct bis-oxa/thiazoles

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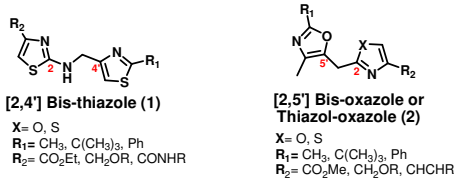
INTRODUCTION

Natural products play an important role in drug development, particularly in anticancer, antibiotics and antiparasitics drugs.[1] [2,4'] or [2,5'] Bis-1,3-oxa/thia-aza scaffolds are present in numerous structures of marine natural products with interesting biological actvities.[2] As examples, we cited Bengazoles, Laucamides and Largazole.

As part of our search for compounds as candidates for anticancer or antiparasitic drugs employing molecular simplification,[3] we are interested in an efficient methodology to synthesize bis-1,3-oxa/thiaaza like bis-thiazole (**1**, figure 1) and bis-oxazoles or oxazol-thiazole (**2**, figure 1).

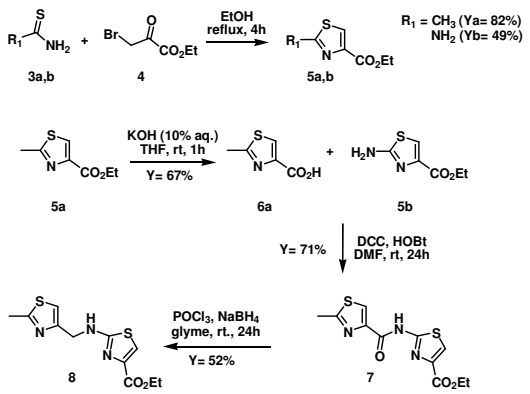
Figure 1: Bis-1,3-oxa/thiaza systems



RESULTS AND DISCUSSION

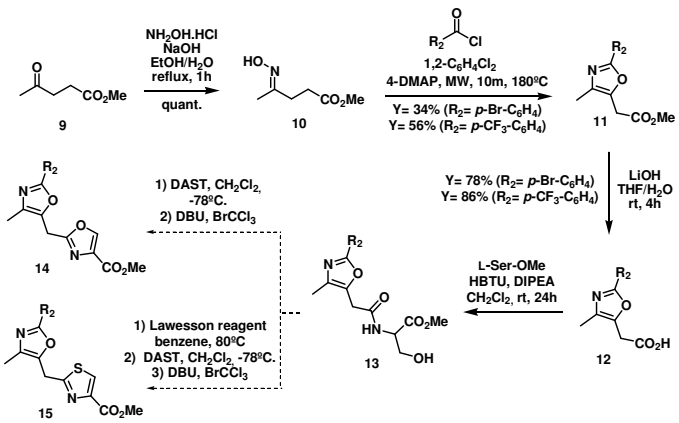
Bis-thiazoles of type **1**, were prepared as is shown in scheme 1 employing Hantzsch's methodology to obtain thiazole **6** and then, using coupling agents to prepare the amide **7.** The reduction method reported by Kuehne,[4] allowed us to obtain the thiazoles linked by a methylenamine bridge.

Scheme 1: Synthesis of [2,4'] bis-thiazole.



In order to prepare bis-oxazoles or oxazol-thiazole of type **2**, we started synthesizing the trisubstituted oxazole **11** employing cyclocondensation cascade of oximes and acyl chlorides as was described by Wipf.[5] Using ethyl levulinate **9** as starting material it was possible to obtain only oxazoles containing an ester group with aromatic at R_2 substituent. Then, ester **11** was hydrolized to the carboxilic acid **12** and coupled with L-serine methyl ester. (Scheme 2)

Scheme 2: Synthesis of [2,5'] bis-oxazoles or [2,5'] thhiazol-oxazole.



The amides **13** are key intermediates to obtain [2,5'] bisoxazole **14** by cyclodehydration and oxidation process or [2,5'] thiazole-oxazole **15** by using Lawesson reagent and then cyclodehydative agent and oxidation reactions.

Compounds **7**, **8,** **14** and **15** will be submitted to anthelmintic assay.

CONCLUSION

The methodology to prepare bis-thiazoles (**1**) results a rapid and efficient strategy to generate molecular diversity by using different starting amides or by modifying bis-thiazol **8** on the ester group.

We are searching an alternative synthetic route to prepare a wide variety of oxazole **11,** so that allows us synthesized diversity at [2,5'] bis-1,3-oxa/thiaaza systems.

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REFERENCES

[1] Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461.
[2] Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464.
[3] Scarone, L.; Fajardo, J.; Saldaña, J.; Domínguez, L.; Espósito, P.; Dematteis, S.; Wipf, P.; Manta, E.; Serra, G. *Lett. Drug, Des. & Disc.* **2009**, *6*, 413 and references cited there.
[4] Kuehne, M.E.; Shannon, P.J. *J. Org. Chem.* **1977**, *42*, 2082.
[5] Wipf, P.; Fletcher, J.M.; Scarone, L. *Tetrahedron Lett* **2005**, *46*, 5463.